Translational MRI in CNS Drug Discovery

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Introduction

The expression "translational" was coined a few years back in medical research, to express the potential benefit that modern technologies may bring to the discovery and to the development of new and improved therapeutic options for the most burning medical needs. As is true for many fashionable terms, the exact meaning of "translational" may vary, depending already on who says it and in which context. One current definition of "Translational Medicine" reads (http://en.wikipedia.org/wiki/Translational_medicine):

> Translational medicine attempts to more directly connect basic research to patient care. (…) In the case of drug discovery and development, translational medicine typically refers to the "translation" of basic research into real therapies for real patients. The emphasis is on the linkage between the laboratory and the patient's bedside. (…) Many pharmaceutical companies are building translational medicine groups to facilitate the interaction between basic research and clinical medicine, particularly in clinical trials. Traditionally, basic research has been separated from the clinical practice of medicine by a series of hurdles or fences. New drugs were developed independent of the clinic, and often "thrown over the fence" for safety testing and clinical trials. The move toward translational medicine is focused on removing these fences, and stimulating "bench to bedside" research.

This is the typical definition of "forward translation." Equally important, however, is the complementary route "from bedside to bench": how can the experience and the technologies available in clinical centers be best capitalized on, in order to direct and to enrich preclinical drug research? How can all the information obtained from patient studies be utilized to explore more efficiently the mechanisms of neuropathology and to identify potential new drug targets? A close linkage from clinical research back into early drug discovery will enhance the chances to successfully create new therapies for the ultimate benefit of the patient.

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The various imaging modalities such as CT, US, PET and MRI by their very nature are well suited to enhance the translational bridges to and fro preclinical drug discovery and clinical development: they can be applied equally well both in human patients and in animal models of disease. The same imaging read-outs that eventually will demonstrate efficacy in a clinical trial can be utilized to assess the action of new compounds in animal models. Vice versa, the experience gained by imaging in animals will help to increase the confidence in image measures and will facilitate and accelerate the discovery and the validation of innovative imaging biomarkers.

In the past decade, many pharmaceutical companies have invested in preclinical imaging laboratories, in order to enhance their drug discovery programs. In this chapter, the value as well as some possible pitfalls of "translational imaging" will be elucidated with tangible examples from two domains, Alzheimer's disease (AD) and psychiatric disorders.

Translational Imaging in Alzheimer's Disease

The ever increasing number of elder by patients with AD, the associated burden on families and the health care system, the lack of a validated understanding of the underlying pathology, and finally the complete lack of any cure make AD a (dismal) textbook example for the potential value of translational imaging markers in the discovery and development of new therapeutic concepts. The slow progression of the disease and its high variability render conventional clinical trials very tedious and expensive, to the point of being impractical: when using some clinical cognitive rating scale as the endpoint to demonstrate the benefit of a new medical entity, hundreds of patients need to be enrolled in a year-long trial before the possible efficacy in patients can be assessed. Any marker providing a more quantitative and reliable insight into the disease process and predicting future progression in the patient would significantly enhance the process of elaborating new treatment concepts against this devastating disease. The availability of similar tools for preclinical pharmaceutical research would accelerate the assessment of potential new targets and innovative approaches to modulate the pathologic pathway, prior to testing new medical entities in humans. Before analyzing the applications of MRI techniques in transgenic mouse models of the disease, the following section very briefly reviews the main MRI approaches pursued in AD patients.

Clinical Imaging in AD patients

The objectives of current imaging approaches in AD patients fall in two, conceptually fundamentally different categories. The imaging protocols in the first category aim at finding (early!) indicators of the progression of the disease, correlating with the clinical status. Such a marker would serve not only as a predictor for the future

evolution of the disease in a patient by enhancing the diagnostic accuracy but would also have the potential to serve as an objective marker to assess treatment efficacy. If some imaging read-out in Alzheimer patients would reflect, for instance, neuronal integrity, and if one could demonstrate that neuronal loss is stopped by some new medical entity, the confidence to test this treatment in a larger clinical trial would be significantly enhanced, to assess the ultimate clinical benefit for the patients.

The second category of the imaging approaches strives to obtain mechanistic rather than diagnostic insight: these modalities assess parameters in the specific pathologic pathways involved in the disease, without directly reflecting the status of the patient. Such a mechanistic marker can increase the confidence in the concept of a new therapeutic approach by demonstrating that indeed the targeted pathway is modulated by some intervention. This kind of marker, however, provides little or no evidence that the status of the patient will indeed improve after the intervention.

The most prominent example in the first category is three-dimensional anatomical brain imaging to measure the volume of the total brain, of some specific substructures in the brain (typically the entorhinal cortex) or the ventricles. Among others, these approaches have been pioneered by the group of Nick Fox who introduced the boundary-shift-integral to follow the evolution of total brain volume in individual persons (Fox and Freeborough 1997; Scahill et al. 2003; Chan et al. 2003; Fox and Schott 2004), and by Clifford Jack and his team who focused more on measuring the volume of substructures in the brain (Jack et al. 1997; Jack et al. 1998; Grundman et al. 2004; DeCarli et al. 2007). The potential value of these volumetric imaging measures over clinical cognitive tests or rating scales is emphasized by statistical power calculations which show that the required sample size to detect significant effects is much reduced for imaging readouts (Fox et al. 2000; Jack et al. 2003; Jack et al. 2004a; Ezekiel et al. 2004). Finally, a study testing the effects of Donepezil treatment detected a slowing of the rate of hippocampal atrophy (Krishnan et al. 2003). The findings from all these pioneering studies, and the conceptual face value of measuring neuronal loss, were so convincing that volumetric imaging became one of the main pillars in a large public-private partnership initiated by the National Institutes of Health, the "Alzheimer's Disease Neuroimaging Initiative (ADNI)" (http://www.adni-info.org; Jack et al. 2008a). One of the main goals of this initially five-year-long endeavor is to improve the design of clinical trials in AD by generating a large database linking the imaging readouts to the clinical status and progression of patients. Ultimately, the findings and methods validated in this venture should help to lead to effective treatment against the disease.

Another example in the first category is hydrogen magnetic resonance spectroscopy (^{1}H-MRS). One of the main pioneers of ^{1}H-MRS in AD patients is Brian D. Ross who found typical changes in the spectra from AD patients compared to normal, age-matched controls (Miller et al. 1993; Shonk et al. 1995): a reduction of the amplitude of the signal of N-acetyl-aspartate (NAA), most likely reflecting the neuronal loss in the advanced stages of the disease, and an increase of the signal of myoinositol. The relevance of these findings again is increased by the observation of a (temporarily) higher NAA level after treatment with Donepezil in a double-blind, placebo controlled clinical study (Krishnan et al. 2003). Because of the

higher complexity of conducting MRS examinations in a clinical environment, however, the database of spectroscopic studies in human patients as of today is still much slimmer than for volumetric imaging.

The second category of clinical imaging markers in AD includes all the approaches which provide some mechanistic insight into the pathologic process or some treatment effect, but without any measure, which would somehow reflect the patient status. Many of the treatment approaches which are currently pursued in pharmaceutical R&D focus on the amyloid hypothesis, that is, the neurotoxicity induced by the aggregation of amyloid plaques in the patient's brain. Following this hypothesis, any new treatment approach has to demonstrate a decrease of the plaque load in patients in a proof-of-concept study – if the new therapy has no influence on amyloid, no benefit for the patient is conceptually to be expected, and the investment in a phase III trial is not warranted. Plaque load imaging is mainly within the realm of nuclear imaging, using plaque specific ligands carrying isotopes which can be detected either with PET or SPECT-cameras. As of today the best characterized ligand for plaque imaging both in vitro, in animals, and in humans is the "Pittsburgh-compound B (PIB)" [e.g., (Klunk et al. 2003; Jack et al. 2008b)], but there are a number of other ligands in development at various sites which may have different properties, in particular in terms of amyloid binding specificity. In addition, various concepts to use MRI for the direct or indirect visualization of the plaque burden are being explored [e.g., (Benveniste et al. 1999; Poduslo et al. 2002; Higuchi et al. 2005; Bartlett 2005)].

Preclinical MRI in Transgenic Mouse Models of AD

How can these clinical imaging concepts be translated back into preclinical pharmaceutical discovery, exploiting the "bedside-to-bench" route? The first requirement is the availability of some model system which mimics essential aspects of the pathology, and which allows one to examine the action of innovative therapeutic concepts. Once past the early experimental stages in test tubes or Petri dishes, pharmaceutical drug discovery in AD focuses mainly on transgenic mouse models with mutations that generate similar alterations in the mouse brain as the human disease. The creation of these transgenic mouse models follows the experience and the hypotheses gained from clinical research: the rationale behind most transgenic models for AD are based either on the amyloid-hypothesis, the tau-hypothesis, or both [e.g., (Hsiao et al. 1996; Lewis et al. 2000; Ishizawa et al. 2003)]. The purpose of these animal models is to obtain a better understanding of the pathophysiologic pathways of the disease process, to test the effects of potential treatments, and also to develop and to validate new biomarkers ultimately for human use. In particular for the latter two goals, preclinical in vivo imaging plays an essential role. The list of successes and failures in this area also provides more conceptual insight in the huge potential – but also the pitfalls – of translational imaging in pharmaceutical R&D.

The detection of neuronal loss by volumetric brain imaging would be the first obvious approach to phenotype and to characterize these transgenic animal models.

Indeed, some studies have described smaller brain areas in transgenic mice, some even before onset of plaque formation (Weiss et al. 2002; Redwine et al. 2003). Reports on total brain volume are conflicting: a smaller total brain volume – albeit not accompanied by a loss of neurons – has been recently detected in the APP T714I mouse model (Van Broeck et al. 2008), but our own studies have not revealed any significant reduction of total brain volume or ventricle size in PS2APP mice (von Kienlin et al. 2005). Furthermore, these studies showed one clear distinction between mice and man: whereas the healthy human brain reaches its largest size in late adolescence and then starts shrinking, the brain of mice grows continuously throughout their life span (see Fig. 1). In mice, any mechanism of neuronal loss thus may be compensated or masked by the natural growth of the organ. Unless tissue atrophy can reliably be detected in some specific transgenic mouse model and can – with high confidence – be associated to some specific pathologic mechanism, preclinical volumetric brain imaging has low translational value.

The second-best characterized parameter in human AD patients is magnetic resonance spectroscopy (MRS) to characterize the neuron-chemical profile. MRS has also been applied in transgenic mouse models and has detected differences between transgenic animals to controls [e.g., (von Kienlin et al. 2005; Dedeoglu et al. 2004)]. These studies reported lower levels of NAA and Glutamate in the frontal cortical areas of aged transgenic mice; these findings are consistent with reduced neuronal viability and in line with the findings in human AD patients. Although this change of the metabolic profile is significant and may provide further insight into the disease pathology, it has to be recognized that its value for preclinical

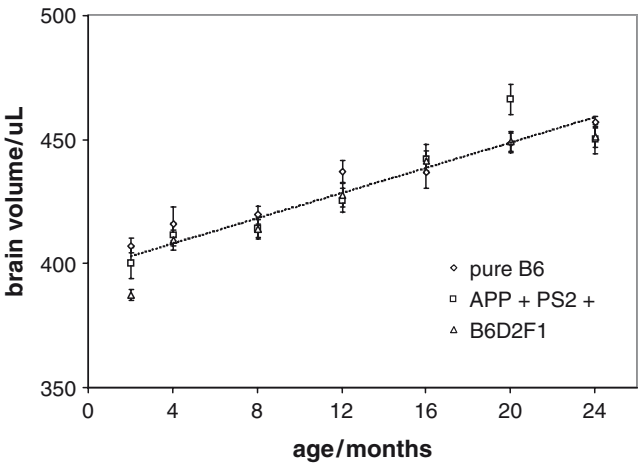

Fig. 1 Growth of murine whole brain volume throughout the lifespan, monitored by volumetric MRI in a transgenic mouse model for Alzheimer's disease (PS2APP), and in two wild-type control strains (pure B6 and B6D2F1). In contrast to the human brain which reaches its maximal size in early adulthood, the brain of mice grows continuously. This growth may mask potential brain atrophy induced by neurodegeneration–no difference in the rate of total brain growth could be detected between these three strains

drug discovery is limited for practicality reasons: the amyloid pathology in the PS2APP mice starts early and leads to behavioral deficits already detectable at age 8 months (Richards et al. 2003), but the reduction of NAA in the MR spectrum reaches significance only after an age of 16 months. The duration of studies testing the effect of new compounds using MRS as read-out thus is in the range of at least one year, which is prohibitive in the usual time-frame of preclinical discovery departments.

Functional imaging appears to be very promising to characterize the phenotype of transgenic animals. PET or SPECT imaging consistently detects hypo-metabolism or reduced blood flow, respectively, in particular in the temporoparietal cortex of AD patients [review in (Johnson and Albert 2000)]. It is still under debate whether this is due to some vascular impairment or a reduced neuronal energy demand – the "hen-or-egg" question. Translating these findings into the preclinical research environment, the Novartis group – among others – has run some very interesting studies in the transgenic mouse strain APP23: first, they have shown age dependent, progressive cerebrovascular abnormalities which may contribute to the pathogenesis of the disease; from the absence of transgene overexpression or amyloid plaque in the vasculature, they concluded that the vascular deficit might be because of the deleterious effects of soluble A-beta (Beckmann et al. 2003). In addition, in a functional study stimulating the somatosensory cortex, they found the hemodynamic response decreasing with age, which they attributed to a compromised cerebrovascular reactivity in this disease model (Mueggler et al. 2003). In the B6.PS2APP model, we could also detect consistent hypoperfusion in the dorsal parts of the cortex as early as from age 10 months (Weidensteiner et al. 2008). If these findings are confirmed and further validated, these functional parameters may become early markers of the pathologic status of the animals, and thus serve as potential readouts for functional improvement when testing the efficacy of new compounds.

The second category of imaging approaches defined above provides mechanistic insight into the disease pathology; in this category, for instance, all methods to visualize amyloid plaques in vivo, in the brain of transgenic mice (Wadghiri et al. 2003; Jack et al. 2004b; Vanhoutte et al. 2005; Braakman et al. 2006) belong. High-field MRI instruments and modern coil technology have improved the sensitivity to the point that individual larger plaques can be detected through MR microscopy. It nevertheless needs to be recognized that the data acquisition time required to achieve sufficient spatial resolution is still quite long. Furthermore, other imaging modalities such as optical imaging may be better suited to measure plaque load in small rodents (Hintersteiner et al. 2005).

Translational MR Imaging in Psychiatric Disorders

A second domain in CNS drug R&D in which translational imaging modalities are playing a critical role is the huge field of psychiatric disorders. Imaging is expected to provide a better understanding of the etiology of these diseases, the

brain areas involved, and the underlying disease mechanisms. This should lead to the development of quantitative imaging markers providing differentiated information about the patient status, markers which are less variable and less subjective than current clinical rating scales. Translational imaging research in psychiatric disorders has been adopted by several pharmaceutical companies as a pragmatic, efficient approach to extend predictivity of animal models and treatment outcomes. These imaging biomarkers are used to assess the efficacy and differentiation of new drug candidates in animal models allowing a more focused, faster early drug development. Neuroimaging findings in schizophrenia, as an example of translational approaches used for psychiatric disorders, are developed in the following sections.

Clinical Imaging in Schizophrenia

Several imaging techniques have been extensively used in schizophrenic patients to better understand pathophysiology and identify new potential biomarkers. Impaired functional connectivity is one of the main brain alterations measured in schizophrenic patients. A large set of data implicates the frontal lobes as key areas involved in this dysfunctional neurocircuitry. fMRI studies reveal dorsolateral prefrontal cortex (DLPFC) and anterior cingulate cortex (ACC) dysfunctions in individuals with schizophrenia (Yoon et al. 2008; Tamminga et al. 1992). This alteration in DLPFC and ACC responses has been associated with impaired attention and cognition. A third cortical subregion, the medial prefrontal cortex (mPFC), was abnormally hyperactive in patients performing socioemotional paradigm, reflecting reality distortion processes (Taylor et al. 2007). Functional abnormalities have not been measured in cortical areas only. Indeed, patients performing a contextual memory task showed neuropathology in frontohippocampal circuitry. Despite similar memory performance, these patients activated neuronal pathways different from healthy individuals (Weiss et al. 2006). Efficacy of antipsychotic treatments on abnormal brain activity was reported in schizophrenic patients. Interestingly, distinct effects were measured with typical and atypical antipsychotics (Braus and Brassen 2005).

In addition to impairment in executive functions (i.e., attention, cognition), schizophrenic patients could present negative symptoms such as anhedonia, a loss of interest or pleasure in daily activities. Anhedonia is associated with dysfunction of the brain reward system. Patients performing a reward-learning association task showed inappropriately stronger activations in the ventral striatum, one of the key brain areas involved in reward processing, consistent with abnormal assignment of motivational salience to neutral stimuli (Jensen et al. 2008). Abnormal ventral striatum activity was also measured during an incentive monetary task in medication-free schizophrenics. In this study, the reduced striatal activity during presentation of reward- and loss-indicating stimuli correlated with the severity of symptoms (Juckel et al. 2006).

To better understand neuropathology, schizophrenia-like symptoms could be induced in healthy volunteers. Indeed, pharmacological challenges with glutamatergic

N-methyl-D-aspartate (NMDA) receptors antagonists such as ketamine or phencyclidine (PCP) induce in healthy humans symptoms that resemble schizophrenia and exacerbate them in patients (Umbricht et al. 2000; Lahti et al. 2001; Krystal et al. 2003). A recent pharmacological magnetic resonance imaging study measuring blood oxygenation level dependent (BOLD) signal changes during ketamine administration in healthy humans reveals selective regional brain activity changes (Deakin et al. 2008). The author describes a ketamine-induced activity decrease in ventromedial frontal cortex (i.e., orbitofrontal cortex, subgenual cingulate) and increase in areas such as mid-posterior cingulate cortex, thalamus, or temporal cortical regions. These effects were reversed by pharmacological treatment. Indeed, attenuation of neuropsychiatric effects and dysfunctional neuronal circuitry of ketamine have been shown in healthy volunteers treated with lamotrigine, a sodium channel blocker that decreases glutamate release (Deakin et al. 2008; Anand et al. 2000). Ketamine could be an attractive translational pharmacological challenge to assess neuronal circuitry involved in NMDA antagonist-induced schizophrenia symptoms and to evaluate potential antipsychotic efficacy.

As schizophrenia is a neurodevelopmental disease, anatomical connectivity could be an important marker for disease progression and efficacy of therapeutics. Diffusion tensor magnetic resonance imaging (DTI) noninvasively assesses neuronal tractography, that is, abnormal circuitry, neuronal degeneration or demyelination. Indeed, DTI studies consistently suggest altered intra- and interhemispheric connectivity in schizophrenic patients such as corticocortical, frontotemporal and transcallosal altered connectivity (Seal et al. 2008; Brambilla and Tansella 2007). Further investigations are needed to better characterize neuropathology and evaluate effects of antipsychotic treatments.

Another translational neuroimaging technique is magnetic resonance spectroscopy (MRS), allowing measurement of brain metabolites. In schizophrenic patients, the main reported alteration is a reduced NAA level in the temporal and frontal lobes and in the thalamus. Such a reduction in NAA level is considered as surrogate of neuronal loss or dysfunction and correlates with increased symptoms (Callicott et al. 2000; Ende et al. 2000). In addition to this effect, higher cortical level of glutamate has been measured in schizophrenia (Olbrich et al. 2008). Interestingly, antipsychotic treatments normalized such alterations in metabolites levels. For example, atypical antipsychotic treatments such as clozapine or risperidone showed efficacy by increasing NAA levels in both cortical areas and in the thalamus (Ertugrul and Uluğ 2007; Bertolino et al. 2001; Szulc et al. 2005; Braus et al. 2001). Lower NAA levels measured in patients under typical medication may be caused by either the progression of the disease or by a direct action of these drugs (Bustillo et al. 2001). However, more recent evidence showed no direct "toxic" effect of typical antipsychotics such as haloperidol on NAA concentrations (Bustillo et al. 2007). MRS technique could also be used to assess effect of pharmacological challenges. An increase in anterior cingulate glutamine, a putative marker of glutamate release, was indeed measured in healthy humans treated with ketamine (Rowland et al. 2005).

Preclinical MRI in Animal Models of Schizophrenia

Within the last few years, numbers of preclinical neuroimaging studies have emerged in the field of psychiatry. Indeed, brain alterations in animal models of schizophrenia have been evaluated and compared to human findings. A variety of animal models of schizophrenia have been developed that are aimed at gaining a better understanding of the etiology and pathophysiology of this disorder. These models are classically divided into two broad categories – the pathophysiological models, relying on deficits induced by abnormal neurodevelopment, dysfunction of cortical glutamatergic systems, or genetic susceptibility and the neuropharmacological models related to specific neurotransmitter systems (typically dopamine and glutamate) and postulating that a dysfunction of these systems is underlying the disease. The neuropharmacological models rely on the use of psychotomimetic substances (dopamine agonists, NMDA antagonists) to produce schizophrenic-like symptoms in animals. In both types of models, similar schizophrenia-like symptoms are generated such as hyperlocomotion, sensorimotor deficits, or deficits in latent inhibition, impaired performance in cognition and memory tasks, and altered social and reward processes (Le Pen et al. 2002; Lipska and Weinberger 2000).

Similar functional brain alterations have been measured in a neurodevelopmental and a pharmacological animal model of schizophrenia (Risterucci et al. 2005). Indeed, rodents with neonatal ventral hippocampal lesion or acutely treated with the NMDA antagonist PCP showed abnormal activity in corticosubcortical circuitry involving brain areas such as temporal and prefrontal cortex, ventral striatum, or thalamus. This dysfunctional activity in regions that may play a role in schizophrenia-related behavior of rats, are reminiscent of neuroimaging findings in schizophrenic patients. Specificity of dysfunctional neurocircuitry was demonstrated as antipsychotic drugs like olanzapine, haloperidol, and risperidone normalized the PCP-induced activity changes whereas no reversal was measured with the anxiolytic diazepam (unpublished observation). Similar findings were reported by other groups. Indeed, dysfunctions in cortico-limbo-thalamic regions were measured in PCP- and ketamine-treated animals (Gozzi et al. 2008; Littlewood et al. 2006). The authors showed efficacy of the antipsychotic clozapine in the PCP model (Gozzi et al. 2008). Interestingly, as described by Deakin's group in healthy volunteers (Deakin et al. 2008), the anticonvulsant lamotrigine suppressed NMDA antagonist-induced activity changes in rodents as well (Gozzi et al. 2008). NMDA receptor antagonist models offer a good translational approach to evaluate efficacy of new potential antipsychotic drugs. They offer reasonable face validity with respect to the clinical disorder, and predict to some degree the efficacy of drugs in patients (Large 2007). As these pharmacological models are related to specific neurotransmitter systems, it is essential to combine findings from different animal models to increase construct validity for schizophrenia. MRI appears to be a valid noninvasive tool to improve translation between preclinical and clinical findings, to better understand brain alterations in schizophrenia, and to establish early markers for successful treatment.

Pharmacological MRI studies could also be done in naïve animals to identify brain signature of specific drug treatments (Nordquist et al. 2008). Activity profile of a new drug (i.e., activity changes measured in a network of brain areas) could be compared to antipsychotics profiles. This information could help to better understand the mechanism of action and further extend predictivity of treatment outcomes.

Anatomical connectivity can also be assessed in animals. DTI recently allowed the evaluation of early postnatal development of rat brain (Bockhorst et al. 2008). This technique has a great potential to evaluate white matter integrity in neurodevelopmental models of schizophrenia. Translation to human was not yet demonstrated as no DTI study has been reported in animal models of psychiatric disorders.

Alterations in brain metabolites have been shown in animal models of schizophrenia. For example, MRS revealed reduced NAA levels in prefrontal cortex of adult rats with neonatal hippocampal damage (Bertolino et al. 2002). This finding correlates with decreased NAA levels measured in frontal areas in schizophrenic patients (Callicott et al. 2000). Translational aspect should be further evaluated using pharmacological treatment.

Conclusion

Translational aspects are a critical element in the design of preclinical imaging studies for drug discovery. Taking clinical expertise and the imaging protocols that are applied in human patients into account will enrich preclinical experimentation and will facilitate the consistent interpretation of data across species. The main issue that is consistently raised when exploring new potential imaging markers, however, is about appropriate validation: how much confidence is required to trust that data obtained in animals are predictive of the human situation? In most CNS disorders – with multiple sclerosis being the possible exception confirming the rule – the relationship between imaging findings and patient status has not been established. For years to come, it is very unlikely that the health authorities will accept any imaging read-out as "surrogate," that is, as primary endpoint in phase III trials for CNS disorders. In disorders such as AD, for which no efficacious treatment is available, no "positive control" data can be generated for assessing the statistical power of the imaging modality, that is, its signal amplitude and its variability. The level of confidence in the imaging protocol thus depends on the face value of the measurement concept–insight in a well-known disease mechanism will generate much more convincing results than exploratory studies which merely provide some correlation to the (patho-) physiologic status of the patient. The main value of clinical imaging for pharmaceutical R&D lies in mechanistic proof-of-concept studies during phases I and II, and in adjunct studies such as for dose finding.

In our aging population, slowly developing chronic disorders without efficacious treatment options, such as neurodegenerative diseases or psychiatric disorders and also diabetes, arthritis etc., are a major concern for the people and a threat for the

health care system. In particular the slow progression of these disorders makes clinical trials very long and costly before demonstrating the benefit of some new potential treatment. Proof-of-concept imaging studies in human patients will have an essential role in deciding which projects will be carried forward to full clinical development. Similarly, translational preclinical studies providing mechanistic insight into drug effects in animal model systems will generate the confidence as to which compounds will be moved into man. They also serve to identify and to validate innovative imaging approaches as early, quantitative, and statistically more powerful biomarkers. The better characterization of the in vivo properties of new medical entities will reduce the attrition rate in pharmaceutical portfolios and will enhance the discovery of better treatment options for the most urgent medical needs. High expertise in the concepts and the execution of translational imaging studies constitutes a significant competitive advantage for pharmaceutical companies.

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